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AB In vivo models have shown that tissue-restricted antigen may be captured by bone marrow-derived cells and cross-presented for the **tolerization** of CD8+ T cells. Although these studies have shown peripheral **tolerization** of CD8+ T cells, the mechanism of antigen transfer and the nature of the antigen-presenting cell (APC) remain undefined. We report here the establishment of an in vitro system for the study of cross-**tolerance** and show that **dendritic** cells (DCs) phagocytose **apoptotic** cells and **tolerize** antigen-specific CD8+ T cells when cognate **CD4**+ T helper cells are absent. Using this system, we directly tested the "two-signal" hypothesis for the regulation of priming versus **tolerance**. We found that the same CD83+ myeloid-derived DCs were required for both cross-priming and cross-**tolerance**. These data suggested that the current model for peripheral T cell **tolerance**, "signal 1 in the absence of signal 2", requires refinement: the critical checkpoint is not DC maturation, but instead the presence of a third signal, which is active at the DC-**CD4**+ T cell interface.

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14, 12, 9, 6, 4, 3, 2, 1??